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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,293	01/09/2001	Thomas E. Wagner	035879-0116	5976

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EXAMINER	
LI, QIAN J	
ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,293	WAGNER ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2002* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 23-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group III in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-13 and 23-28 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claims 14-22 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention commensurate to its scope.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 14, 18, and 19 recite a method of preparing a hybrid cell comprising bringing at least two different cells into contact under conditions that promote cell fusion and then purifying the resultant hybrid without antibiotic or metabolic selection. Given the broadest reasonable interpretation, the claims are drawn to a process that embraces *any* condition or method that causes cell fusion, *any* method that identifying, selecting, and purifying *any* hybrid cell.

In view of the guidance provided, the specification teaches that fusion-promoting conditions are well known to the artisan, and typically involve the addition of an agent that promotes cell fusion; exemplary useful agents are polymeric compounds like polyethylene glycols. (Last paragraph in page 9). The specification teaches that one aspect of the invention is accomplished with the aid of at least two different dyes, the method may entail separately contacting, each with a different dye, the two cell types to

be fused. This pre-fusion labeling marks each cell with a different dye, and permits discrimination among each fusion parent cell and the hybrid fusion product, thus, the hybrid fusion product may be separated from the reactant cells by fluorescence activated cell sorting (FACS).

However, the specification fails to teach conditions other than polyethylene glycols that could induce cell fusion, and it fails to teach purification methods other than FACS. The specification does not allow the skilled artisan recognize that applicants are in possession of invention in scope with the claims at the time of the instant filing.

The claims are obvious generic to many known or largely unknown methods of preparing hybrid cells. In analyzing whether the written description requirement is met for the claimed subject matter as a genus of methods that promoting cell fusion and a genus of methods that purifying fusion cells without antibiotic or metabolic selection, a representative number of species has to be disclosed by their method steps, by the name of the well-known methods, or by naming agents used in the methods. With regard to the written description requirement for a method claim, it requires an adequate description for the materials and method steps essential for the practice of the invention.

Considering potential conditions and methods, known or unknown, which encompassed by the recited invention, the exemplary embodiment is not the representative species of the genus. For example, *Ohkohchi et al* (Lasers Surg Med 2000;27:262-8) teach a method for inducing cell fusion by laser radiation, which is not known at the time of instant filing date.

Applicant is referred to the Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or using it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *all* or representative species of conditions that promote cell fusion and methods that purify a hybrid cell without antibiotic or metabolic selection. Therefore, only the described polyethylene glycols and fluorescent FACS meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 14-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

These claims are directed to a method of preparing a hybrid cell comprising bringing at least two different cells into contact under conditions that promote cell fusion and then purifying the resultant hybrid without antibiotic or metabolic selection. Given the broadest reasonable interpretation, the claims embrace any method that causes cell fusion and any method that identifying, selecting, and purifying any hybrid cell.

However, as discussed in the Written Description section above, the specification fails to provide an adequate written description for the broad scope of the claims. In view of the state of the art and the levels of the skilled in the pertinent art, as indicated in PTO-1449 and cited in the following sections, numerous publications use fluorescent dyes, cyanine dyes, and combination of antibody and fluorescent & cyanine dyes for tracing, identifying, and purifying among different cell populations and hybrid cells (*Koolwijk et al*, *Horen et al*, *Deka et al*, and *Gong et al*). Without knowing what are the methods other than the cited ones, the skilled artisan would not know how to practice the invention commensurate to its scope.

Therefore, in view of the nature of the invention, the guidance provided, and the breadth of the claims, one of skilled in the art could not practice the invention without extensive undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is vague and indefinite because the claim is incomplete. The method provides for preparing a hybrid cell comprising a step "purifying the resultant hybrid without antibiotic or metabolic selection", however, the claim does not set forth any positive step for recited purification, thus, it is unclear how the cells are purified. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claim 15 recites the limitation "said purification". There is insufficient antecedent basis for this limitation in the claim.

Claims 14 and 15 are vague and indefinite. Claim 14 recites a two-step hybrid cell preparation method including cell fusion and purification, claim 15, which depends from claim 14, recites a further step of labeling each of fusion partner cells with a different fluorescent dye, it is unclear when the labeling occurs. From the teaching of the specification such labeling is done before the fusion and purification, but the claims read on an event that may occur after. For examining purpose, it is interpreted as labeling the cells before the fusion.

Claim 18 is vague and indefinite because it recites "purifying the resultant hybrid

cell in less than 48 hrs". The meaning of the recitation could be interpreted as the purification process takes less than 48 hours or the cells are purified within 48 hours from the starting point of fusion. Further, it seems "under" is missing after "contact" in line 2.

The recitation of "under conditions that promote cell fusion" (claims 14, 18, 19) is vague and indefinite because the claims do not make clear what are the conditions that promote cell fusion, the recitation implies latent properties of the condition, it is unclear what are these properties, and therefore, the meets and bounds of the claims are unclear.

The recitation of "an antigen presenting cell that lacks an accessory factor required to generate a positive immune response" (claims 16 and 21) is vague and indefinite because the claims and the specification do not make clear what is the recited accessory factor, the recitation implies latent properties of the cells, it is unclear what are and how one may identify these properties, therefore, the meets and bounds of the claims are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14-19 are rejected under 35 U.S.C. 102(b) as being anticipated by *Koolwijk et al* (Hybridoma 1988;7:217-225).

These claims are directed to a method of preparing a hybrid cell comprising bringing at least two different cells into contact under conditions that promote cell fusion and then purifying the resultant hybrid without antibiotic or metabolic selection; wherein the method comprising labeling each of different cells with a different fluorescent dye, and purifying by FACS, wherein said hybrid cell comprises at least one cell selected from the group consisting of a macrophage, a dendritic cell, and an antigen presenting cell, a tumor cell, and a normal cell; wherein the purification is done in less than 48 hours. In claim 19, the method is clearly set out as contacting a first and a second cell with a different dye, conducting fusion and purification.

Koolwijk et al teach a method of preparing a hybrid cell, hybrid hybridomas, comprising contacting a first hybridoma cell with a green fluorescent, contacting a second hybridoma cell with a red fluorescent, fusing the cells with polyethylene glycol 4000. The double-fluorescent stained cells were sorted by FACS and purified by Percoll density gradient centrifugation (see pages 218-219). The hybridoma cells are composed of tumor cells and B lymphocytes, which is a type of antigen presenting cells. Although *Koolwijk et al* do not specify a time frame, they use the same fusion and seletion technique taught in the specification, thus, it is assumed that it takes less than 48 hrs. In the absence of evidence to the contrary, *Koolwijk et al* anticipate the instant claims.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by *Wagner et al* (Cytogenet Cell Genet 1997;76:172-5).

Wagner et al teach purifying hybrid cells in the absence of the normal chromosome 17 by PCR typing, Southern blot analysis, and FISH. Thus, *Wagner et al* anticipate the instant claim.

Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by *Lespagnard et al* (PTO-1449, A31).

Claim 18 recites a method comprising bringing two different cells into contact under conditions that promote cell fusion and purifying the resultant hybrid cell in less than 48 hours.

Lespagnard et al teach a method comprising fusing dendritic cells with mastocytoma cells and purifying the cells in less than 48 hrs (abstract and Flow cytometry section on page 252). Thus, *Lespagnard et al* anticipate the instant claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Koolwijk et al* (Hybridoma 1988;7:217-225) as applied to claims 14-19 above, further in view of *Horen et al* (US 4,859,584, IDS) and *Deka et al* (US 6,197,593).

Koolwijk et al teach selecting and purifying the fused cells by labeling fusion partner cells with different fluorescent dyes as discussed above. *Koolwijk et al* do not teach cyanine dyes.

Horen et al teach the type of long chain cyanine dyes that are less toxic to cells, stable in viable cells, and staining the cell membrane of variety of cells, thus more suitable for *in vitro* and particularly *in vivo* use (columns 1 & 2). *Deta et al* teach that cyanine dyes (SYTO and TOTO serials) could be used for distinguishing between different cell populations (abstract and figures).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Koolwijk et al*, by simply substituting the red and green fluorescents with now available cyanine dyes as taught by *Horen et al and Deta et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because the recited advantage of cyanine dyes. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 14-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Koolwijk et al* (Hybridoma 1988;7:217-225), *Horen et al* (US 4,859,584, IDS) and *Deka*

et al (US 6,197,593) as applied to claims 14-22 above, further in view of *Gong et al* (Nature 1997;3:558-561, IDS).

Koolwijk et al, Horen et al, and *Deka et al* teach purifying the hybrid cells by labeling fusion partner cells with different fluorescent dyes, particularly cyanine dyes as discussed above. *Koolwijk et al, Horen et al*, and *Deka et al* do not teach a particular fusion among dendritic cells and tumor cells.

Gong et al teach fusion between dendritic cells and carcinoma cells for antitumor activity. *Gong et al* use fluorescent labeled antibody for cell selection.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the methods taught by *Koolwijk et al*, *Horen et al*, and *Deka et al* in the process for purification of dendritic-tumor cell hybrids with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the various methods available in the art using the choice of dyes for purification of cells of interest. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
April 19, 2002

JAMES KETTER
PRIMARY EXAMINER